Asymmetric amination of cyclic β-keto esters catalyzed by amine-thiourea bearing multiple hydrogen bonding donors

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Abstract
Highly efficient asymmetric amination of cyclic β-keto esters with dialkyl azodicarboxylates has been achieved by bifunctional amine-thiourea bearing multiple hydrogen bond donors. Catalyst **1d** showed excellent results for this transformation and provide optically active α-amino acid derivatives in up to 96% ee. Multiple hydrogen bond donors play a significant role in accelerating reactions and improving enantioselectivities.

Keywords: Amination, asymmetric catalysis, organocatalyst, enantioselectivity, β-keto esters

Introduction

Optically active α-amino acid derivatives are prevalent in many natural alkaloids, compounds of pharmaceutical significance, and biologically important building blocks in organic synthesis.[1] The asymmetric amination of β-keto esters with azodicarboxylates provides an efficient approach for the construction of α,α-disubstituted amino acid derivatives containing a nitrogen-substituted quaternary stereocenter,[2] and much attention has been paid to developing enantioselective catalytic protocols for this reaction over the past decade. Highly efficient Cu^{II}/Ph-BOX and Cu^{II}/trisoxazoline complexes catalyzed amination reaction of β-keto esters has been reported by Jørgensen and Gade.[3] Shibasaki developed a Ln^{III}/amide catalytic system to carry out this reaction with high reactivity and excellent enantioselectivity.[4] Recently, asymmetric organocatalysis becomes a powerful and environmentally friendly methodology for the catalytic production of the valuable synthetic building blocks and has received much attention.[5] Cinchona alkaloid derivatives perform good to excellent reactivities and enantioselectivities for asymmetric amination of β-keto esters, β-keto lactones[6] and α-cyanoesters.[7] Takemoto's bifunctional thiourea catalyst exhibited excellent catalytic activity for this amination reaction.[8] Axially chiral guanidines and quaternary phosphonium phase-transfer

catalysts have also been designed and applied successfully for this transformation by Terada and Maruoka.[9]

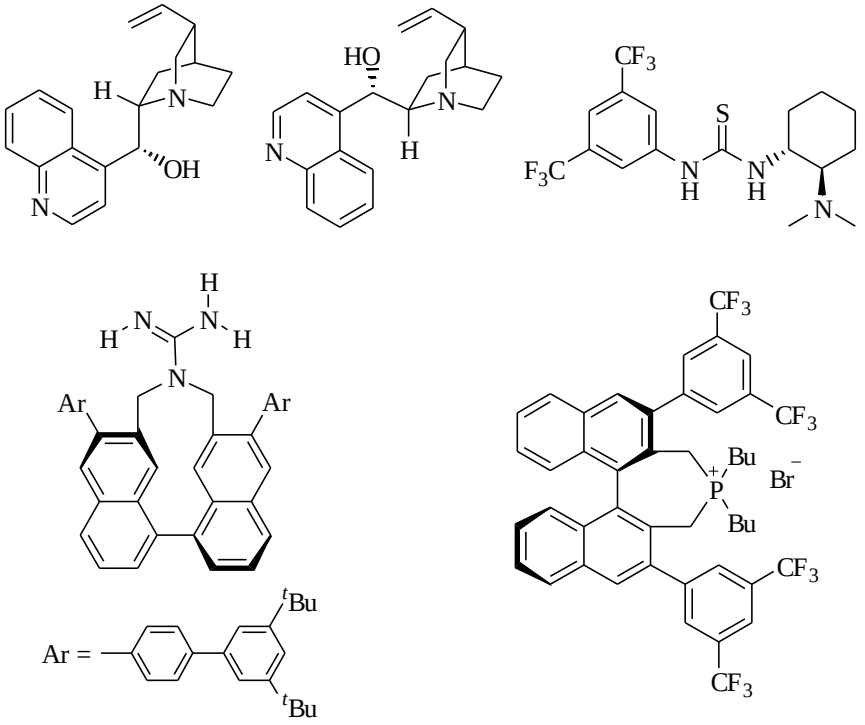


Figure 1. Examples of some organocatalysts for asymmetric amination of β-keto ester.

Recently, we reported a new class of bifunctional amine-thiourea catalysts **1** bearing multiple hydrogen bond donors, which showed excellent performances in catalytic asymmetric Michael addition and nitro-Mannich reaction.[10] Extending the interest of these organocatalysts in asymmetric catalysis, herein we report that oganocatalyst **1d** shows excellent results for asymmetric amination of cyclic β-keto esters with azodicarboxylates and provides optically active α,α-disubstituted amino acid derivatives in up to 97% ee.

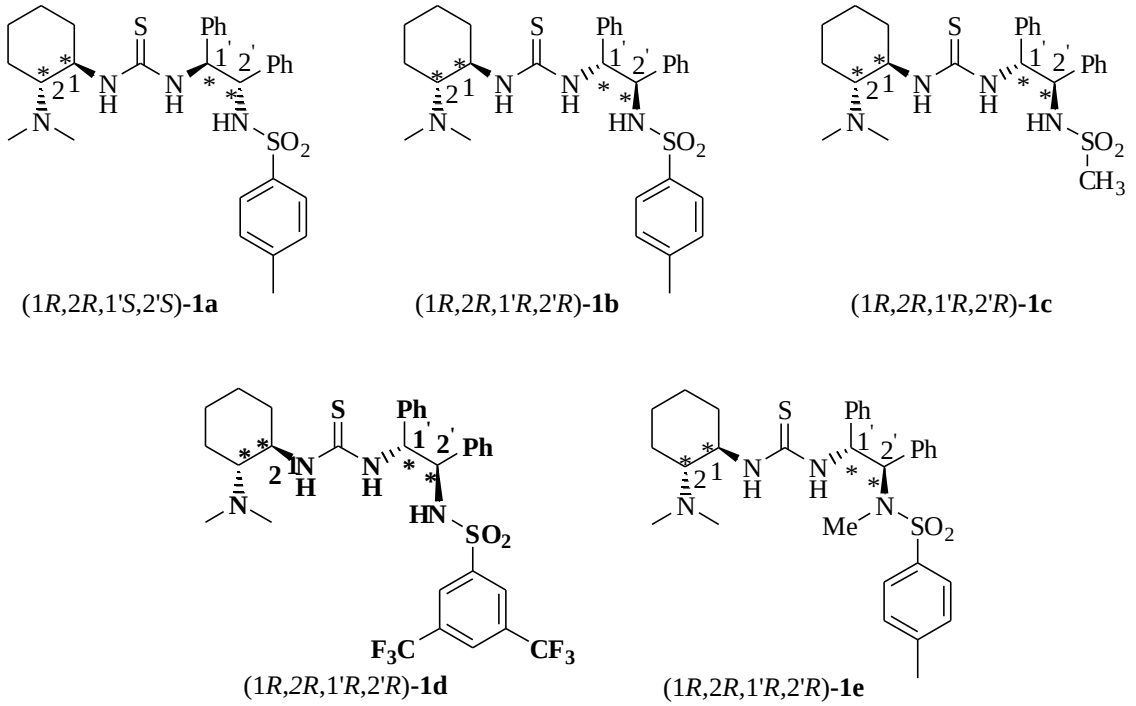


Figure 2. Amine-thioureas bearing multiple hydrogen bond donors.

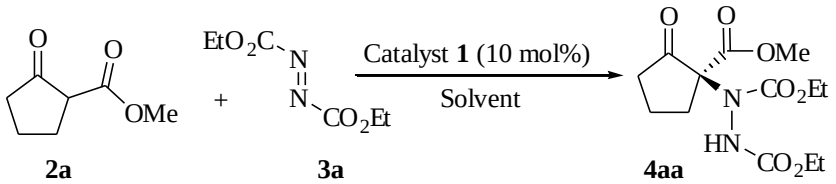
Results and Discussion

Our initial investigation began with the amination of methyl 2-oxo-cyclopentanecarboxylate **2a** and diethyl azodicarboxylate **3a**, and the representative results are summarized in Table 1.

To our delight, the reaction was finished in less than 10 min at room temperature in the presence of 10 mol% fine-tunable multiple-hydrogen-bond-donor catalysts **1a-d** (Table 1, entries 1-4). Among the catalysts tested, (1*R*,2*R*,1'*R*,2'*R*)-**1d** bearing two electron-withdrawing CF_3 groups on the aromatic ring of sulfonamide $NHSO_2Ar$ revealed to be the most efficient catalyst (Table 1, entry 4), which was consistent with the results achieved in the study of the Michael addition and the nitro-Mannich reaction.[10] Much lower enantioselectivity was observed by the methylated (1*R*,2*R*,1'*R*,2'*R*)-**1e** as the catalyst further demonstrated the significant importance of the multiple hydrogen bond donors embedded in the catalysts on the reactivity and enantioselectivity (Table 1, entry 6). The catalyst loading is crucial for the reproducibility of the experiment. The enantioselectivity decreased from 81% to 54% when the catalyst loading was reduced from 10mol% to 5 mol% (Table 1, entrie 4 and 5).[11] A preliminary screening of solvent effects showed that EtOAc, THF and ether were the solvents of choice; other solvents such as DCM, PhMe, CH_3CN, DMSO gave lower enantioselectivities (Table 1, entries 4 and 7-12). Protic solvents such as ^{i}PrOH or EtOH produced almost racemic adducts (Table 1, entries 13 and 14), which could be ascribed to the unfavorable background reaction[6] or the competitive

activation of 3a between catalyst **1d** and the protic solvent. Reducing the temperature to -78 ºC led to a complete reaction with a remarkable improvement of enantioselectivity (Table 1, entries 15 and 16).

Table 1. Screening studies of asymmetric amination of methyl 2-oxocyclopentanecarboxylate **2a** with diethyl azodicarboxylate **3a** catalyzed by multiple-hydrogen-bond-donor organocatalysts **1**[a]

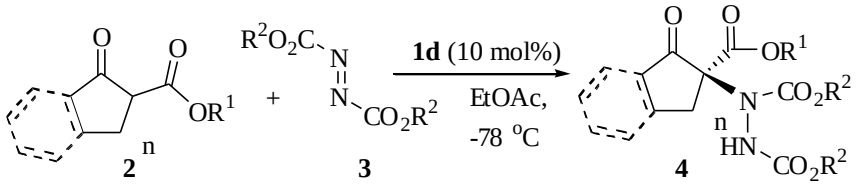


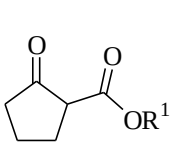
2a **3a** **4aa**

Entry	Catal.	solvent	T (ºC)	time (min)	yield (%)[b]	ee (%)[c,d]
1	**1a**	EtOAc	rt	10	94	68
2	**1b**	EtOAc	rt	10	96	73
3	**1c**	EtOAc	rt	10	96	76
4	**1d**	EtOAc	rt	10	95	81
5	**1e**	EtOAc	rt	30	91	54
6	**1d**	EtOAc	rt	60	96	43
7	**1d**	THF	rt	10	93	79
8	**1d**	Et_2O	rt	10	95	80
9	**1d**	PhMe	rt	10	95	67
10	**1d**	DCM	rt	30	92	41
11	**1d**	MeCN	rt	20	88	42
12	**1d**	DMSO	rt	10	91	20
13	**1d**	PrOH	rt	10	86	0
14	**1d**	EtOH	rt	10	92	0
15	**1d**	Et_2O	-78	60	94	92
16	**1d**	EtOAc	-78	60	95	95

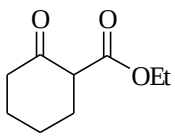
[a]Unless otherwise noted, the reaction was performed with 0.10 mmol of **1a** and 0.125 mmol of **2a** in 0.5 mL of solvent. [b]Isolated yield. [c]Enantiomeric excesses were determined by chiral HPLC analysis. [d]The absolute configurations of the product was determined as S by comparing the optical rotation and HPLC retention time with the reported date. [7e]5 mol% catalyst was used.

Table 2. Enantioselective amination of various β-ketoesters **2** with dialkyl azodicarboxylates **3** catalyzed by organocatalyst **1d**[a]

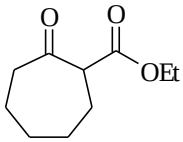




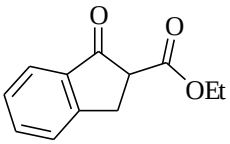
2a: R^1 = Me;
2b: R^1 = Et;
2c: R^1 = ^{i}Pr;
2d: R^1 = ^{t}Bu;



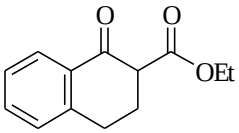
2e



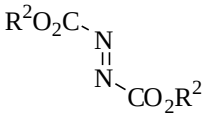
2f



2g



2h

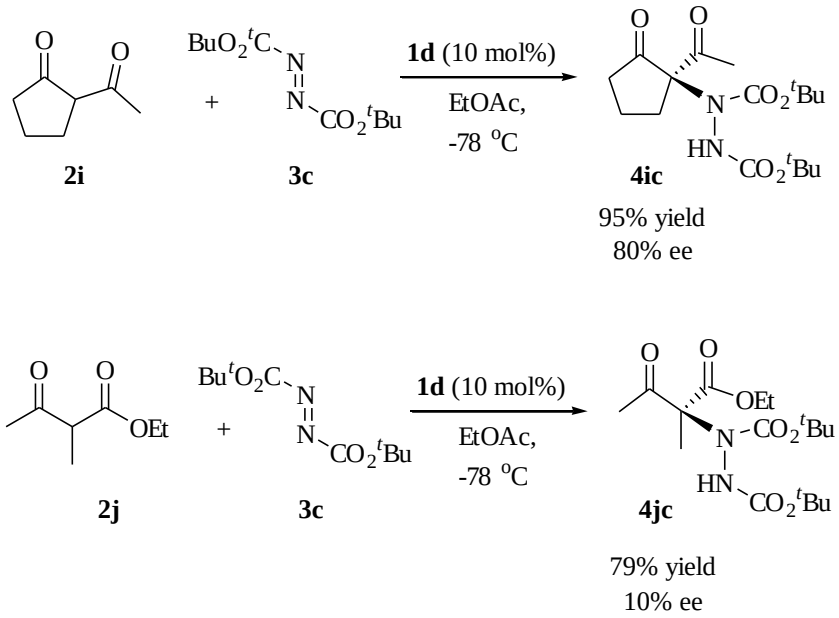


3a: R^2 = Et;
3b: R^2 = ^{i}Pr;
3c: R^2 = ^{t}Bu;

Entry	**2**	**3**	Prod. **4**	time (h)	yield (%)[b]	ee (%)[c]
1	**2a**	**3a**	**4ab**	1	98	95
2	**2a**	**3b**	**4ab**	1	96	96
3	**2a**	**3c**	**4ac**	1	96	95
4	**2b**	**3b**	**4bb**	1	97	97
5	**2c**	**3b**	**4cb**	3	95	93
6	**2d**	**3b**	**4db**	3	98	94
7	**2b**	**3c**	**4bc**	3	97	94
8	**2c**	**3c**	**4cc**	6	95	90
9	**2e**	**3a**	**4ca**	10	88	73
10	**2f**	**3a**	**4fa**	1.5	91	74
11	**2g**	**3c**	**4ge**	3	86	76
12	**2h**	**3a**	**4ha**	3	94	69

[a]Unless otherwise noted, the reaction was performed with 0.10 mmol of **2**, 0.125 mmol of **3** in 0.5 mL of EtOAc. [b]Isolated yield. [c]Enantiomeric excesses were determined by chiral HPLC analysis. [d]The absolute configurations of the product was determined as *S* by comparing the optical rotation and HPLC retention time with the reported date.[7]

Having established the optimal reaction conditions, the scope of this amination reaction was investigated, and the results are summarized in Table 2. First, we examined the effect of the ester substituent of the azodicarboxylates. The results show that the steric hindrance of the ester groups has no influence on the enantioselectivities, and excellent ee ranging from 95% to 96% were observed for all the tested azodicarboxylates, which was opposite to the trend exhibited by Takemoto's thiourea catalyst (Table 2, entries 1-3). Subsequently, the effect of the ester functional group of 2-oxo-cyclopentanecarboxylate **2** was also investigated for this transformation. Although no obvious differentiation of enantioselectivity was observed when the ester functional group of **2** switched from methyl to ethyl, *iso*-propyl or *tert*-butyl, the bulky ester functional group such as *iso*-propyl and *tert*-butyl has a detrimental effect on the reactivity and renders an extended reaction time (Table 2, entries 2 and 4-6). Catalyst **1d** could also affect the asymmetric amination of both six- an seven-membered ring substrates **2e** and **2f**, although moderate enantioselectivities were achieved (Table 2, entries 9 and 10). Bicyclic β-keto esters **2g** and **2h** were also tolerated in this reaction, and the corresponding adducts could be obtained in high yields with 76% and 69% ee, respectively (Table 2, entries 11 and 12). The results for asymmetric amination of cyclic β-keto esters are comparable to those obtained with chiral metal catalysts or organocatalysts.[3-9]



Scheme 1. Asymmetric amination of 2-acetyl-cyclopentanone **2i** and ethyl 2-methyl-3-oxo-butylate **2j** with dialkyl azodicarboxylate.

The asymmetric amination of 2-acetylcyclopentanone was also investigated. As shown in scheme 1, the desired adduct **4ia** was generated in 95% yield with 80% ee under the optimized reaction condition. However, only 10% ee was achieved when acyclic β-keto ester **2jc** was applied in this system.

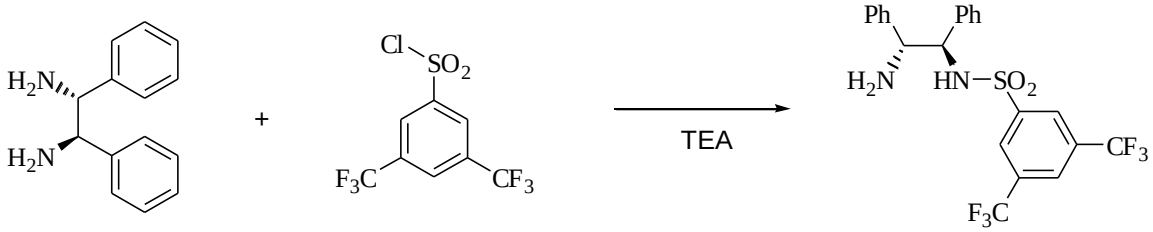
Conclusions

In summary, we have described a highly efficient asymmetric amination of cyclic β-keto esters with dialkyl azodicarboxylates catalyzed by bifunctional amine-thiourea catalyst bearing multiple hydrogen bond donors. Catalyst **1d** exhibits the best performance for this transformation and provides optically active α-amino acid derivatives in up to 96% ee. Multiple hydrogen bond donors play a significant role in accelerating reactions and improving enantioselectivities. Future investigation of those bifunctional organocatalyst in other asymmetric reactions is ongoing in our laboratory and will be reported in due course.

Experimental Section

General. ^{1}H NMR spectra were recorded on a VARIAN Mercury 300 MHz spectrometer in chloroform-d_3. Chemical shifts are reported in ppm with the internal TMS signal at 0.0 ppm as a standard. The data are reported as (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or unresolved, brs = broad singlet, coupling constant(s) in Hz, integration). ^{13}C NMR spectra were recorded on a VARIAN Mercury 75 MHz spectrometer in chloroform-d_3. Chemical shifts are reported in ppm with the internal chloroform signal at 77.0 ppm as a standard. Commercially obtained reagents were used without further purification. All reactions were monitored by TLC with silica gel-coated plates. Enantiomeric ratios were determined by HPLC, using a chiralpak AS-H column, a chiralpak AD-H column or a chiralcel OD-H column with hexane and *i*-PrOH as solvents.

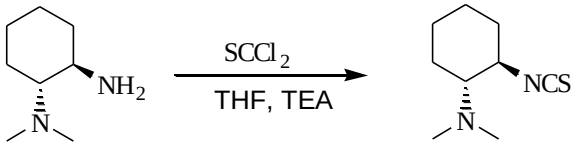
Synthesis of *N*-((1*R*,2*R*)-2-amino-1,2-diphenylethyl)-3,5-bis(trifluoromethyl)-benzene-sulfonamide



A solution of 3,5-bis(trifluoromethyl) benzenesulfonyl chloride (312.6 mg, 1 mmol) in anhydrous THF (5 mL) was added dropwise to (1*R*,2*R*)-1,2-diphenylethane-1,2- diamine (212.3mg, 1mmol), triethylamine (277 mL, 2 mmol) and anhydrous THF (10 mL) with ice-cooling. The reaction mixture was brought to room temperature and stirred over night. The result solution was diluted with ethyl acetate and washed with brine. The resulted organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash silica gel chromatography. The pure product was obtained as a white solid in 86% yield. Mp. 158-160 °C; $[R]^{25}_{D}$ +15.6 (*c*, 0.4, $CHCl_3$); IR (KBr) 3436, 3355, 3298, 1352, 1278, 1265, 1196, 1163, 1128

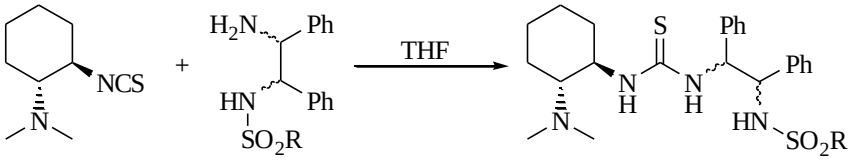
cm^{-1}; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 4.18 (d, *J* = 4.5 Hz, 1H), 4.52 (d, *J* = 4.5 Hz, 1H), 7.13 (s, 10H), 7.79 (s, 1H),7.86 (s, 2H); ^{13}C NMR ($CDCl_3$, TMS, 75 MHz) δ 60.27, 63.68, 125.69, 126.42, 127.17, 127.32, 128.10, 128.18, 128.76, 132.17, 132.62, 138.27, 141.15, 143.40; HRMS Calcd. for $C_{22}H_{19}F_6N_2O_2S$: 489.1071, found: 489.1047;

Synthesis of (1*R*,2*R*)-2-isothiocyanato-*N*,*N*-dimethylcyclohexanamine



Thiophosgene (1.86 mL, 24.4 mmol) was added dropwise to a solution of (1*R*,2*R*)-*N*,*N*-dimethylcyclohexane-1,2-diamine (2.31 g, 16.3 mmol) and triethylamine (6.77 mL, 48.8 mmol) with ice-cooling. The reaction mixture was stirred for about 4h, and TLC analysis indicated completion of the reaction. Then the reaction mixture was concentrated *in vacuo*, and the residue was purified by flash silica gel chromatography to afford brown oil in 91% yield. $[\alpha]^{25}_D$ -99.0 (*c* 0.36, $CHCl_3$); IR (KBr) 2935, 2860, 2827, 2780, 2185, 2095, 1618 cm^{-1}; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 1.16-1.25 (m, 4H), 1.69-1.84 (m, 3H), 2.15-2.19 (m, 1H), 2.34 (s, 6H), 2.40-2.47 (m, 1H), 3.51-3.59 (m, 1H); ^{13}C NMR ($CDCl_3$, TMS, 75 MHz) δ 23.58, 24.32, 24.45, 33.57, 40.41, 58.23, 67.22, 76.63, 77.06, 77.48; MS (EI) *m/z* 184 ($[M]^{+\cdot}$).

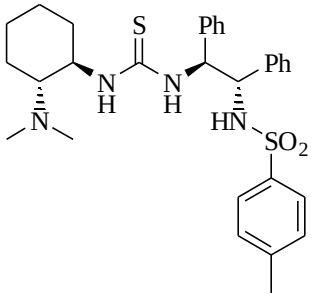
General procedure for the synthesis of organocatalysts (1a-1d)



1a-1d

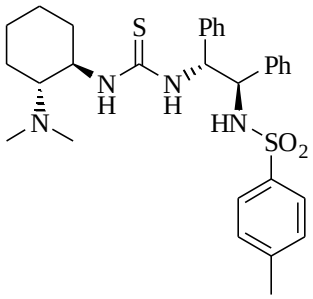
To a solution of corresponding sulfonamide (1 mmol) in anhydrous THF (10 mL) was added (1*R*,2*R*)-2-isothiocyanato-*N*,*N*-dimethylcyclohexanamine (194 mg, 1.05 mmol) at room temperature. The solution was stirred overnight. TLC analysis indicated completion of the reaction. The reaction mixture was concentrated *in vacuo*. The residue was purified by flash silica gel chromatography.

1-((1*R*,2*R*)-2-(Dimethylamino)cyclohexyl)-3-((1*S*,2*S*)-1,2-diphenyl-2-(tosylamino)ethyl) thiourea (1a)



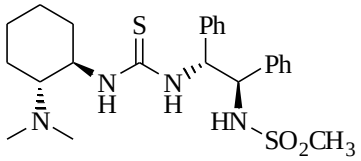
The pure product was obtained as a white solid in 95% yield. Mp. 110-113 °C; $[\alpha]^{25}_{D}$ +18.5 (*c* 0.62, $CHCl_3$); IR (KBr) 3357, 3062, 3030, 2932, 2858, 1536, 1327, 1155 cm^{-1}; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 1.08-1.29 (m, 4H), 1.63-1.76 (m, 3H), 1.95 (s, 6H), 2.20 (m, 1H), 2.25 (s, 3H), 2.42 (m, 1H), 3.58 (m, 1H), 4.70 (d, *J* = 10.2 Hz, 1H), 5.68 (m, 1H), 6.86-7.13 (m, 12H), 7.41 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, TMS, 75 MHz) δ 21.59, 22.37, 24.79, 25.17, 33.41, 40.13, 56.67, 62.99, 63.84, 67.25, 127.10, 127.40, 128.03, 128.13, 128.68, 129.18, 138.21, 138.50, 142.54, 183.00; HRMS Calcd. for $C_{30}H_{39}N_4O_2S_2$: 551.2514, found: 551.2494.

***N*-((1*R*,2*R*)-2-(3-((1*R*,2*R*)-2-(Dimethylamino)cyclohexyl)thioureido)-1,2-diphenylethyl)-4-methylbenzenesulfonamide (1b)**



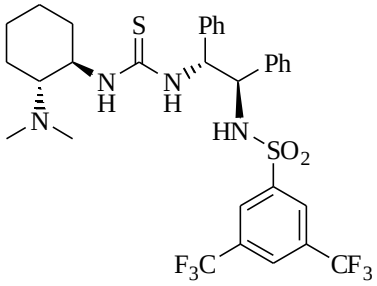
The pure product was obtained as a white solid in 80% yield. Mp. 128-130 °C; $[\alpha]^{25}_{D}$ +3.5 (*c* 0.62, $CHCl_3$); IR (KBr) 3355, 3061, 3030, 2932, 2859, 1538, 1454, 1329, 1157 cm^{-1}; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 1.18-1.27 (m, 4H), 1.68-1.90 (m, 3H), 2.30 (s, 1H), 2.35 (s, 6H), 2.20-2.43 (m, 2H), 3.47 (s, 1H), 4.72 (d, *J* = 10.8 Hz, 1H), 5.81 (m, 1H), 6.86-7.21 (m, 12H), 7.40 (d, *J* = 10.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, TMS, 75 MHz) δ 21.67, 22.88, 24.76, 25.11, 32.89, 41.29, 56.85, 63.04, 64.79, 67.17, 126.99, 127.37, 127.95, 128.10, 128.67, 129.28, 138.46, 142.62, 182.70; HRMS Calcd. for $C_{30}H_{39}N_4O_2S_2$: 551.2514, found: 551.2499.

***N*-((1*R*,2*R*)-2-(3-((1*R*,2*R*)-2-(Dimethylamino)cyclohexyl)thioureido)-1,2-diphenylethyl)methanesulfonamide (1c)**



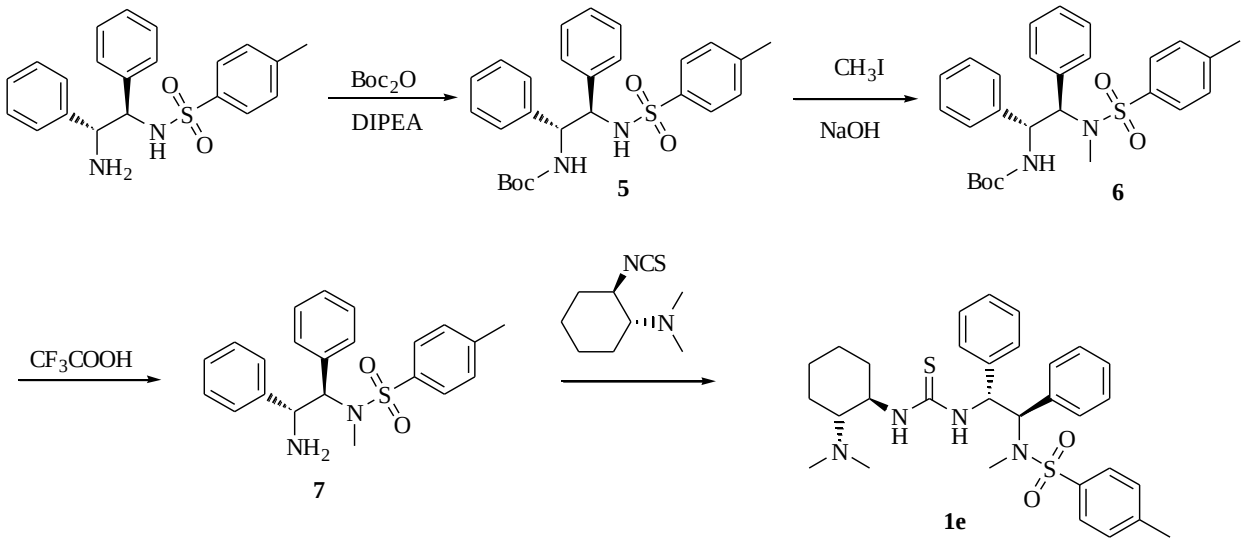
The pure product was obtained as a white solid in 97% yield. Mp. 108-110 °C; $[\alpha]^{25}_{D}$ +9.4 (*c* 0.44, $CHCl_3$); IR (KBr) 3356, 3062, 2931, 2858, 1545, 1320, 1148 cm^{-1}; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 1.21-1.24 (m, 4H), 1.69-1.90 (m, 4H), 2.20 (m, 1H), 2.41 (s, 6H), 2.47 (s, 3H), 3.70 (m, 1H), 4.79 (d, *J* = 10.2 Hz, 1H), 5.88 (s, 1H), 7.08-7.22 (m, 10H); ^{13}C NMR ($CDCl_3$, TMS, 75 MHz) δ 22.65, 24.37, 24.52, 32.59, 39.86, 41.69, 55.24, 62.25, 64.38, 66.34, 127.64, 127.76, 128.44, 128.54, 138.22, 139.15, 183.50; HRMS Calcd. for $C_{24}H_{35}N_4O_2S_2$: 475.2201 , found: 475.2168.

***N*-((1*R*,2*R*)-2-(3-((1*R*,2*R*)-2-(Dimethylamino)cyclohexyl)thioureido)-1,2-diphenylethyl)-3,5-bis(trifluoromethyl)benzenesulfonamide (1d)**



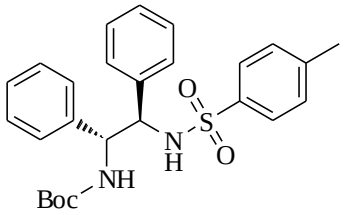
The pure product was obtained as a white solid in 99% yield. Mp. 168-170 °C; $[\alpha]^{25}_{D}$ +43.6 (*c* 0.34, $CHCl_3$); IR (KBr) 3423, 2936, 1541, 1539, 1279, 1162, 1141 cm^{-1}; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 1.20 (m, 4H), 1.71-1.94 (m, 3H), 2.18 (m, 1H), 2.42 (s, 6H), 2.44 (m, 1H), 3.35 (m, 1H), 4.81-4.86 (m, 1H), 5.87 (m, 1H), 6.86-7.12 (m, 10H), 7.71 (s, 1H),7.83 (s, 2H); ^{13}C NMR ($CDCl_3$, TMS, 75 MHz) δ 24.65, 24.98, 24.76, 33.00, 41.77, 60.34, 63.04, 63.98, 65.39, 67.79, 120.79, 124.41, 125.26, 125.59, 126.49, 127.20, 127.88, 128.03, 128.25, 128.40, 128.73, 128.86, 131.89, 132.35, 136.97, 137.76, 144.45, 183.27; HRMS Calcd. for $C_{31}H_{35}F_6N_4O_2S_2$: 673.2106, found: 673.2058.

Synthesis of *N*-((1*R*,2*R*)-2-(3-((1*R*,2*R*)-2-(dimethylamino)cyclohexyl)thioureido)- 1,2-diphenylethyl)-*N*,4-dimethylbenzenesulfonamide (1e)



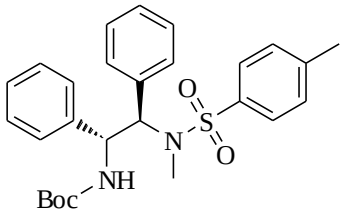
5 **6** **7** **1e**

Synthesis of *tert*-butyl (1*R*,2*R*)-1,2-diphenyl-2-(tosylamino)ethylcarbamate (5)



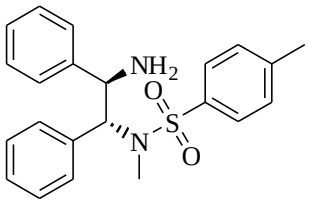
A solution of Boc_2O (94.3 mg, 0.432 mol) in anhydrous dichloromethane (10 mL) was added to (1*R*,2*R*)-1,2-diphenyl-*N*-tosylethane-1,2-diamine (144 mg, 0.393 mmol) and DIPEA (74.3 µL, 0.432 mmol) in anhydrous dichloromethane (20 mL) with ice-cooling. After the addition, the reaction mixture was brought to room temperature and stirred overnight. TLC analysis indicated completion of the reaction. The reaction mixture was concentrated *in vacuo*. The residue was purified by flash silica gel chromatography. The pure product was obtained as a white solid in 90% yield. Mp. 167-170 °C; $[\alpha]^{25}_D$ +13.0 (*c* 0.78, $CHCl_3$); IR (KBr) 3390, 3312, 2928, 1686, 1514, 1158 cm^{-1}; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 1.45 (s, 9H), 2.30 (s, 3H), 4.56-4.61 (m, 1H), 4.78-4.84 (m,1H), 5.33 (br, 1H), 6.22 (br, 1H), 6.78-6.81 (m, 2H), 6.96-7.02 (m, 7H), 7.14-7.15 (m, 3H), 7.43 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, TMS, 75 MHz) δ 21.62, 28.57, 60.23, 64.16, 80.79, 127.11, 127.54, 12769, 128.03, 128.22, 128.72, 129.33, 138.08, 138.57, 142.88, 156.55; HRMS Calcd. for $C_{26}H_{30}N_2O_4S+Na^+$: 489.1824, found: 489.1827.

Synthesis of *tert*-butyl (1*R*,2*R*)-2-(*N*-methyl-*N*-tosylamino)-1,2-diphenyl ethylcarbamate (6)



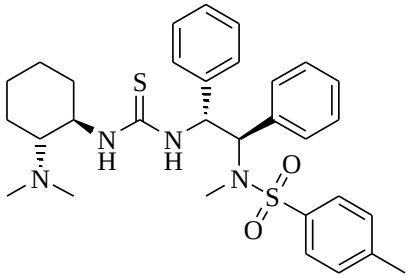
Methyl iodide (220 µL, 3.54 mmol) was added to a solution of *tert*-butyl (1*R*,2*R*)-1,2-diphenyl-2-(tosylamino)ethylcarbamate (165 mg, 0.35 mmol) and 1N NaOH (0.4 mL) in 1,4-dioxane (2 mL) at room temperature. TLC analysis indicated completion of the reaction after about 4h. The result solution was diluted with water and extracted with ethyl acetate. The resulted oil phase was washed with brine, dried with Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash silica gel chromatography. The pure product was obtained as a white solid in 81% yield. Mp. 67-69 °C; $[\alpha]^{25}_D$ -30.4 (*c* 0.54, $CHCl_3$); IR (KBr) 3428, 2975, 2928, 1711, 1599, 1508, 1384, 1163 cm^{-1}; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 1.43 (s, 9H), 2.36 (s, 3H), 2.80 (s, 3H), 5.20 (m, 1H), 5.32 (m, 1H), 5.45 (br, 1H), 6.94-7.20 (m, 12H), 7.58 (d, *J* = 6.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, TMS, 75 MHz) δ 21.69, 28.59, 30.07, 54.18, 64.67, 80.00, 127.34, 127.64, 127.79, 128.28, 128.37, 128.68, 129.33, 129.79, 134.73, 137.56, 140.20, 143.39, 155.81; HRMS Calcd. for $C_{27}H_{32}N_2O_4S+Na^+$: 503.1980, found: 503.1926.

Synthesis of (1*R*,2*R*)-*N*-methyl-1,2-diphenyl- *N*-tosylethane-1,2-diamine (7)



Tert-butyl (1*R*,2*R*)-2-(*N*-methyl-*N*- tosylamino)-1,2-diphenylethylcarbamate (60 mg, 0.125 mmol) was added to CF_3COOH (0.43 mL) with ice-cooling. After the addition, the reaction mixture was brought to room temperature and stirred for 2h. TLC analysis indicated completion of the reaction. CF_3COOH was removed *in vacuo*. The residue was washed with saturated $NaHCO_3$ and extracted with ethyl acetate. The combined organic phase was concentrated *in vacuo*. The residue was purified with silica gel chromatography. The pure product was obtained as a white solid in 67% yield. Mp. 130-132 °C; $[\alpha]^{25}_D$ +5.0 (*c* 0.7, $CHCl_3$); IR (KBr) 3382, 1631, 1597, 1383, 1321, 1153, 938 cm^{-1}; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.35 (s, 3H), 2.84 (s, 3H), 4.44 (d, *J* = 10.2 Hz, 1H), 5.25 (d, *J* = 10.2 Hz, 1H), 7.01-7.17 (m, 12H), 7.58(d, *J* = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, TMS, 75 MHz) δ 21.68, 29.84, 55.79, 67.51, 127.57, 127.97, 128.23, 128.60, 129.24, 129.64, 135.87, 137.10, 142.35, 143.35; HRMS Calcd. for $C_{22}H_{24}N_2O_2S+Na^+$: 403.1456, found: 403.1445;

Synthesis of 1-((1*R*,2*R*)-2-(*N*-methyl-*N*-tosylamino)-1,2-diphenylethyl)-3-((1*R*,2*R*)-2 -(dimethylamino)cyclohexyl)thiourea (1e)



To a solution of (1*R*,2*R*)-*N*-methyl-1,2-diphenyl-*N*-tosylethane-1,2-diamine (64 mg, 0.168 mmol) in anhydrous THF (2 mL) was added (1*R*,2*R*)-2-isothiocyanato-*N*,*N*-dimethylcyclohexanamine (34 mg, 0.185 mmol) at room temperature. TLC indicated the completion of the reaction after about 4h. The reaction mixture was concentrated *in vacuo* and purified with silica gel chromatography. The pure product was obtained as a white solid in 78% yield. Mp. 80-82 °C; $[\alpha]^{25}_D$ -25.0 (*c* 0.24, $CHCl_3$); IR (KBr) 3373, 3031, 2929, 2857, 1598, 1540, 1326, 1160 cm^{-1}; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 1.08-1.44 (m, 4H), 1.69-1.91 (m, 3H), 2.22-2.38 (m, 10H), 2.51 (m,1H), 2.87 (s, 3H), 3.87(m, 1H), 5.25 (d, *J*=11.7 Hz, 1H), 6.32-6.39 (dd, *J* =11.1 and 8.1 Hz, 1H), 6.75 (br, 1H), 6.92-7.31 (m, 12H), 7.58(d, *J* = 8.1, 2H); ^{13}C NMR ($CDCl_3$, TMS, 75 MHz) δ 21.76, 24.67, 25.28, 29.92, 30.52, 32.94, 40.07, 54.89, 57.49, 64.97, 66.70, 127.19, 127.62, 128.27, 128.40, 128.60, 129.47, 129.84, 134.22, 137.48, 139.73, 143.60, 181.76; HRMS Calcd. for $C_{31}H_{41}N_4O_2S_2$: 565.2671, found: 565.2582.

General procedure for asymmetric amination of cyclic β-keto esters with dialkyl azodicarboxylates with organocatalyst 1d:
The dialkyl azodicarboxylates **3** (0.104 mmol) in ethyl acetate (0.2 mL) was added to a vial containing cyclic β-keto esters **2** (0.125 mmol) and catalyst **1d** (7 mg, 0.0104 mmol) in ethyl acetate (0.3 mL) at -78ºC. TLC analysis indicated completion of the reaction after about 1-8 h. Then the reaction mixture was concentrated in vacuo to obtain the crude product. The crude product was purified by flash silica gel chromatography to afford the product. **4aa** ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.88 (br, 1H), 4.22-4.28 (m, 4H), 3.86 (s, 3H), 2.75 (m, 2H), 2.40 (m, 2H), 2.11 (m, 1H), 1.78 (m, 1H), 1.30-1.37 (m, 6H); HPLC analysis (Chiralcel AS-H, *i*-PrOH /Hexane = 10/90, flow rate: 1 mL/min, λ = 210 nm, t_{minor} = 24.8 min, t_{major} = 19.3 min, 95% ee.

Acknowledgements

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11. This was probably caused by the unstability of the amine-thiourea catalyst under the reaction condition, which was also observed by Takemoto *et al*, see Ref. 8.

